UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

28/DEC/2005

MEMORANDUM

Subject: Name of Pesticide Product: Dupont Advion Cockroach Bait Arena
EPA Reg. No./File Symbol: 352-AAI
DP Barcode: 323677
Decision No: 362114
PC Code: 067710

From: Tracy Keigwin
Technical Review Branch
Registration Division (7505C)

To: Ann Hangar, RM Team 01
Insecticide Rodenticide Branch
Registration Division (7505C)

Applicant: E.I. Du Pont de Nemours and Company
DuPont Crop Protection
Stine-Haskell Research Center; PO Box 30
Newark, DE 19714

FORMULATION FROM LABEL:

Active Ingredient(s):		% by wt.
067710	Indoxacarb	0.5
Inert Ingredient(s):		99.5
	Total:	100%

ACTION REQUESTED: PM requests review of acute toxicity data for Dupont Advion Cockroach Bait Arena, EPA File Symbol 352-AAI.

BACKGROUND: E.I. Dupont de Nemours and Co., Inc. has submitted 5 acute toxicity studies and one acute inhalation toxicity waiver in support of the registration of EPA File Symbol 352-AAI, Dupont Advion Cockroach Bait Arena. The MRIDs for the 5 submitted studies and the one acute inhalation toxicity waiver are MRIDs 46684604 – 46684609. The studies were conducted at the Haskell Laboratory for Health and Environmental Sciences, Newark, Delaware and Product Safety Labs, Dayton, New Jersey.

Please Note: The test substance used in the submitted studies is referred to as "Indoxacarb (DPX-MP062) 0.5RB". This the generic name for the DuPont Advion Cockroach Bait Arena formulation (e-mail from T. Theodorakis to T. Keigwin, December 1, 2005).

RECOMMENDATIONS: We will accept the rational for the Acute Inhalation Toxicity waiver. This product is a solid formulation that will be (according to the registrant) packaged in "childproof bait stations". We agree that, based on the information provided by the registrant, the acute inhalation toxicity for this product is low and the potential for inhalation exposure limited.

The acute toxicity profile for Dupont Advion Cockroach Bait Arena, EPA File Symbol 352-AAI, is as follows:

acute oral toxicity	IV	Acceptable	MRID 46684604
acute dermal toxicity	IV	Acceptable	MRID 46684605
acute inhalation toxicity	IV	Waiver	MRID 46684609
primary eye irritation	IV	Acceptable	MRID 46684606
primary skin irritation	IV	Acceptable	MRID 46684607
dermal sensitization	Yes	Acceptable	MRID 46684608

PRECAUTIONARY LABELING: The registrant must include sensitization language since this product is a dermal sensitizer. Although not required, we recommend that the registrant include and "IF ON SKIN" First Aid Statement since this product is a dermal sensitizer. Note that the registrant has included some voluntary precautionary language, which is noted in *italics* on the label.

Hazards to Humans and Domestic Animals

CAUTION

Wash thoroughly with soap and water after handling bait stations. Prolonged or frequently repeated skin contact may cause allergic reaction in some individuals.

FIRST AID

IF ON SKIN OR CLOTHING: Take off contaminated clothing. Rinse skin immediately with plenty of water for 15 to 20 minutes. Call a poison control center or doctor for treatment advice.

HOT LINE NUMBER

Have the product container or label with you when calling a poison control center or doctor, or going for treatment. You may also contact 1-800-xxx-xxxx for emergency medical treatment information.

Reviewer: Tracy Keigwin December 15, 2005
Product Manager (EPA): 01

STUDY TYPE: Acute Oral Toxicity - Sprague-Dawley rat; OPPTS 870.1100; OECD 425

TEST MATERIAL (% a.i.): Indoxacarb (DPX-MP062) 0.5RB; Batch number DPX-MP062-428; Lot Number: PLS-14-59; Purity: 0.5% Indoxacarb; brown gel.

CITATION: Finlay, C. Indoxacarb (DPX-MP062) 0.5RB: Acute Oral Toxicity Study in Rats – Up and Down Procedure; Haskell Laboratory for Health and Environmental Sciences, P.O. Box 50, Newark, Delaware; Laboratory project ID: DuPont-16979. July 27, 2005. MRID 46684604. Unpublished.

SPONSOR: E I du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial medicine, Elkton Road, P.O. Box 50, Newark, Delaware 19714

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 46684604), 3 female Crl:CD®(SD)IGS BR albino rats (Source: Charles River Laboratories, Inc., Raleigh, North Carolina; Age: 10-11 weeks; Weight: 197.2 – 220.3) were given a single oral dose of Indoxacarb (DPX-MP062) 0.5RB; Batch number DPX-MP062-428; Lot Number: PLS-14-59; Purity: 0.5% Indoxacarb; brown gel suspended in deionized water at a dose level of 5000 mg/kg. "The rats were dosed one at a time at a minimum of 48 hour intervals". Animals were inspected for mortality and clinical abnormalities at the beginning of fasting, just before dosing (day 0), once during the 30 minutes after dosing, and once each day thereafter. Bodyweights were obtained prior to fasting (day -1) and again on days 0, 7 and 14. A necropsy examination was performed on all test animals.

There was no mortality, and there were no signs of toxicity. Post-sacrifice necropsy results were normal.

Oral LD_{50} Females is greater than 5000 mg/kg. EPA Toxicity Category IV.

This acute oral study is classified as acceptable. It does satisfy the guideline requirement for an acute oral study (OPPTS 870.1100; OECD 425) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Limit Test

Dosing Sequence	Animal No.	Dose level (mg/kg)	24 hour Outcome	14 Day Outcome
1	3653	5000	S	S
2	4226	5000	S	S
3	4228	5000	S	S

S = survival D = death

Statistics - Acute Oral Toxicity (Guideline 425) Statistical Program (Westat, version 1.0, May 2001) was used for all data analyses including: dose progression selections, stopping criteria determinations and/or LD_{50} and confidence limit calculations.

AOT425statpgm (Version: 1.0) Test Results and Recommendations
Acute Oral Toxicity (OECD Test Guideline 425) Statistical Program
Test/Substance: Indoxacarb (DPX-MP062) 0.5RB
Test type: Limit Test
Limit dose (mg/kg): 5000
Assumed LD50 (mg/kg): Default
Assumed sigma (mg/kg): 0.5

DATA:

Test Seq.	Animal ID	Dose (mg/kg)	Short-term Result	Long-term Result
1	3653	5000	O	O
2	4226	5000	O	O
3	4228	5000	O	O

(X = Died, O = Survived)

Dose Recommendation: The limit test is complete.

SUMMARY OF LONG-TERM RESULTS:

Dose	O	X	Total
5000	3	0	3
All Doses	3	0	3

Statistical Estimates:
The LD50 is greater than 5000 mg/kg.

A. Mortality - As listed above.

B. Clinical observations – No test substance related clinical abnormalities were observed during the study. One animal exhibited hair loss and a wound on the paw, however these symptoms were present at the time of dosing.

C. Gross Necropsy – No gross abnormalities were observed at necropsy.

D. Reviewers Conclusions: Agree with the study author in that the Oral LD_{50} in females for Indoxacarb (DPX-MP062) 0.5RB is greater than 5000 mg/kg. EPA Toxicity Category IV. Note: Study is a limit test, rather than an up-and-down procedure.

E. Deficiencies – None

[PC Codes 067710]
EPA REG No. 352-AAI

Reviewer: Tracy Keigwin December 15, 2005
Risk Manager (EPA): 01

STUDY TYPE: Acute Dermal Toxicity - Sprague Dawley Rats; OPPTS 870.1200; OECD 402

TEST MATERIAL (% a.i.): Indoxacarb (DPX-MP062) 0.5RB; Batch number DPX-MP062-428; Lot Number: PLS-14-59; Purity: 0.5% Indoxacarb; brown gel.

CITATION: Finlay, C. Indoxacarb (DPX-MP062) 0.5RB: Acute Dermal Toxicity Study in Rats; Haskell Laboratory for Health and Environmental Sciences, P.O. Box 50, Newark, Delaware; Laboratory project ID: DuPont-16980. July 7, 2005. MRID 46684605. Unpublished.

SPONSOR: E I du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial medicine, Elkton Road, P.O. Box 50, Newark, Delaware 19714

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID 46684605) 5 male and 5 female Crl:CD®(SD)IGS BR albino rats (Source: Charles River Laboratories, Inc., Raleigh, North Carolina; Age: males 9 weeks, females 10 weeks; Weight: males 265.0 – 293.1, females 217.5-237.6g) were dermally exposed to Indoxacarb (DPX-MP062) 0.5RB; Batch number DPX-MP062-428; Lot Number: PLS-14-59; Purity: 0.5% Indoxacarb; brown gel at a dose of 5000 mg/kg bw . "Approximately twenty four hours prior to dosing, the fur of each rat was closely shaved to expose the back from scapular to the lumbar region. On the day of dosing, a 5 cm x 7.4 cm area was delineated with a water insoluble marker and a designated amount of test substance (based on the body weight of each animal) was applied evenly. Test sites were covered with a gauze patch. Test animals were wrapped with a stretch gauze bandage and self adhesive bandage.[4] After 24 hours all binding materials were removed. Excess test substance was removed from the dorsal skin of each rat with warm water and the skin dried with a paper towel. Observations for mortality, signs of toxicity, abnormal behaviour, and dermal irritation were performed daily (excluding weekends for dermal irritation). Bodyweights were taken prior to dosing (day 0) and again on days 7 and 14. A necropsy was performed on all test animals.

There was no mortality, and no test substance related signs were observed. At post-sacrifice necropsy, no gross abnormalities were observed.

Dermal LD_{50} Males = > 5000 mg/kg bw
Dermal LD_{50} Females = > 5000 mg/kg bw
Dermal LD_{50} Combined = > 5000 mg/kg bw

Toxicity based on the lack of mortality observed at the 5000 mg/kg dose level. EPA Toxicity Category IV.

This acute dermal study is classified acceptable. It does satisfy the guideline requirement for an acute dermal study (OPPTS 870.1200; OECD 402) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Dose (mg/kg bw)	Mortality/Number Tested		
	Males	Females	Combined
5000	0/5	0/5	0/10

A. Mortality - as noted in table.

B. Clinical observations – One rat exhibited ocular discharge, although this was not considered test substance related. An additional animal exhibited hair loss. No clinical abnormalities were observed in the remaining 8 animals. "Bodyweight loss of approximately 3% of the day 7 weight occurred in one rat by day 14. No dermal irritation was observed."

C. Gross Necropsy - No gross abnormalities were observed at necropsy.

D. Reviewers Conclusions: Agree with the study author that the dermal LD_{50} for the test substance is greater than 5000 mg/kg.

E. Deficiencies: None

Reviewer: Tracy Keigwin
Risk Manager (EPA): 01

Date: December 15, 2005

STUDY TYPE: Primary Eye Irritation - Rabbit; OPPTS 870.2400; OECD 405

TEST MATERIAL (% a.i.): Indoxacarb (DPX-MP062) 0.5RB; Batch number DPX-MP062-428; Lot Number: PLS-14-59; Purity: 0.5% Indoxacarb; pH = 6; brown gel.

CITATION: Finlay, C. Indoxacarb (DPX-MP062) 0.5RB: Acute Eye Irritation Study in Rabbits; Haskell Laboratory for Health and Environmental Sciences, P.O. Box 50, Newark, Delaware; Laboratory project ID: DuPont-16983. June 17, 2005. MRID 46684606. Unpublished.

SPONSOR: E I du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial medicine, Elkton Road, P.O. Box 50, Newark, Delaware 19714

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID 46684606), 0.1 g of Indoxacarb (DPX-MP062) 0.5RB; Batch number DPX-MP062-428; Lot Number: PLS-14-59; Purity: 0.5% Indoxacarb; pH = 6; brown gel was instilled into the conjunctival sac of the right eye of 3 male New Zealand White rabbits (source: Covance Research Products, Denver, Pennsylvania; Age: young adult; Weight: 2798g - 3123g). The left eye was untreated to serve as a control. Both the treated and untreated eyes remained unwashed. Animals were observed at 1, 24, 48 and 72 hours following instillation. Fluorescein stain examinations were conducted at the 24 hour and each subsequent evaluation. Irritation was scored by the method of Draize.

No positive eye irritation was observed.

In this study, Indoxacarb (DPX-MP062) 0.5RB is not an eye irritant. EPA Toxicity Category IV.

This study is classified as Acceptable. It does satisfy the guideline requirement for a primary eye irritation study (OPPTS 870.2400; OECD 405) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS AND DISCUSSION:

Observations	Number "positive"/number tested			
	Hours			
	1	24	48	72
Corneal Opacity	0 / 3	0 / 3	0 / 3	0 / 3
Iritis	0 / 3	0 / 3	0 / 3	0 / 3
Conjunctivae:				
Redness [a]	0 / 3	0 / 3	0 / 3	0 / 3
Chemosis [a]	0 / 3	0 / 3	0 / 3	0 / 3
Discharge [a]	0 / 3	0 / 3	0 / 3	0 / 3

[a] Score of 2 or more required to be considered positive.

A. Observations - No corneal opacity, iritis or positive signs of conjunctivitis were observed during the study. Please note that the study does record signs of conjunctivitis, however the scores (grade 1) are not considered positive per 870.2400.

B. Reviewers Conclusions: Agree with study author that the test substance is not an eye irritant.

C. Deficiencies - None

[PC Codes 067710]
EPA REG No. 352-AAI

Reviewer: Tracy Keigwin December 15, 2005
Risk Manager (EPA): 01

STUDY TYPE: Primary Dermal Irritation - New Zealand White rabbit; OPPTS 870.2500; OECD 404

TEST MATERIAL (% a.i.): Indoxacarb (DPX-MP062) 0.5RB; Batch number DPX-MP062-428; Lot Number: PLS-14-59; Purity: 0.5% Indoxacarb; brown gel.

CITATION: Finlay, C. Indoxacarb (DPX-MP062) 0.5RB: Acute Dermal Irritation Study in Rabbits; Haskell Laboratory for Health and Environmental Sciences, P.O. Box 50, Newark, Delaware; Laboratory project ID: DuPont-16981. June 2, 2005. MRID 46684607. Unpublished.

SPONSOR: E I du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial medicine, Elkton Road, P.O. Box 50, Newark, Delaware 19714

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 46684607), 3 male New Zealand White rabbits (source: Covance Research Products, Denver, Pennsylvania; Age: young adult; Weight: 2643 - 3016g) were dermally exposed to Indoxacarb (DPX-MP062) 0.5RB; Batch number DPX-MP062-428; Lot Number: PLS-14-59; Purity: 0.5% Indoxacarb; brown gel. Animals were shaved from the scapular to the lumbar region of the back. "One animal was initially treated. When no skin corrosion occurred, 2 additional animals were treated to complete the test". An application of 0.5 g of the test substance was applied to a 6 cm^2 test site on the shaved area. Test sites were covered with a 2-ply, 1 inch square gauze secured to the animal by non-irritating tape. The trunk of each rabbit was wrapped with porous tape. The tape was further secured with waterproof tape. After 4 hours all binding materials were removed and the test sites washed with warm water and patted dry. Animals were observed for 1, 24, 48, 72 hours after patch removal.

All scores for erythema and edema were zero.

In this study, Indoxacarb (DPX-MP062) 0.5RB is not considered to be irritating to the skin. EPA Toxicity Category IV. PDI = 0.0.

This study is classified as acceptable. It does satisfy the guideline requirement for a primary dermal irritation study (OPPTS 870.2500; OECD 404) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Rabbit	Observations	**Hours**			
		1	24	48	72
97/M	Erythema	0	0	0	0
	Edema	0	0	0	0
100/M	Erythema	0	0	0	0
	Edema	0	0	0	0
101/M	Erythema	0	0	0	0
	Edema	0	0	0	0

A. Observations – No animals (0/3) exhibited erythema or edema at any time during the study.

B. Results - PDII – 0.0

C. Reviewers Conclusions – Agree with the study author that the test substance is not irritating to the skin.

D. Deficiencies - None

Reviewer: Tracy Keigwin December 15, 2005
Risk Manager (EPA): 01

STUDY TYPE: Dermal Sensitization – Guinea Pigs; OPPTS 870.2600; OECD 429

TEST MATERIAL (% a.i.): Indoxacarb (DPX-MP062) 0.5RB; Batch number DPX-MP062-428; Lot Number: PLS-14-59; Purity: 0.5% Indoxacarb; brown gel

CITATION: Moore, G. Indoxacarb (DPX-MP062) 0.5RB: Dermal Sensitization Test - Buehler method. Product Safety Laboratories. Dupont Laboratory Study Number 16982. August 2, 2005. MRID 46684608. Unpublished

SPONSOR: E I du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial medicine, Elkton Road, P.O. Box 50, Newark, Delaware 19714

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID 46684608) with Indoxacarb (DPX-MP062) 0.5RB; Batch number DPX-MP062-428; Lot Number: PLS-14-59; Purity: 0.5% Indoxacarb; brown gel, 34 male Hartley albino guinea pigs (preliminary irritation - 4 animals; test group - 20 animals; naive control group - 10 animals) were tested using the method of Buehler (Source: Elm Hill Breeding Labs, Chelmsford , MA; Age: young adult; weight: 311-401g at study initiation). Based on an initial screening with 4 males it was determined that an 100% concentration would be appropriate for the induction and 75% w/w mixture would be appropriate for the challenge. "Body weights were recorded prior to the first induction and on the day after challenge patch removal."

During the main test, 12/20 test animals exhibited very faint (grade 0.5) erythema during induction. Following challenge, 10/20 test animals exhibited faint erythema (grade 1) and 3/20 test animals exhibited moderate erythema (grade 2) at the 24 hour observation. At the 48 hour observation, 4/20 animals continued to exhibit faint erythema and 2/20 animals moderate erythema. At the 24 hour observation, 4/10 naive control animals exhibited very faint erythema. At the 48 hour observation only 1/10 naive control animals continued to exhibit very faint erythema. The test substance did not affect body weight gain.

The procedures were validated within 6 months of this study using undiluted HCA at induction and 75% w/w mixture of HCA in mineral oil at challenge. At both the 24 and 48 hour observations, 4/9 positive control animals exhibited very faint erythema (grade

0.5) and 4/9 positive control animals exhibited faint erythema (grade 1.0) at challenge. Three of the five naive control animals used in the validation study exhibited very faint (grade 0.5) at the 24 hour observation, persisting in 1/5 animals at the 48 hour observation.

In this study, Indoxacarb (DPX-MP062) 0.5RB is considered a dermal sensitizer.

This study is classified as acceptable. It does satisfy the guideline requirement for a dermal sensitization study (OPPTS 870.2600; OECD 406, 429) in the Guinea pig .

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. PROCEDURE

A. Induction – Induction applications occurred once each week for 3 weeks. On the day prior to induction fur was removed from the dorsal and flank area with animal clippers. "At study initiation, a dose of 0.4 g of undiluted test substance was applied to the left side of each test animal using an occlusive 25 mm Hill Top Chamber. The chamber was secured in place and wrapped with non-irritating with adhesive tape to avoid dislocation of the chambers and minimize test substance loss". After 6 hours all binding materials were removed and the test sites cleansed to remove any residual test substance. At 24 and 48 hours after each induction the application sites were scored for signs of erythema.

B. Challenge – "Twenty seven days after the first induction dose, 0.4 g of a 75% w/w mixture of the test substance in distilled water was applied to a naive site on the right side of each animal as a challenge dose using the procedures described above". The irritation response was noted at 24 and 48 hours after application.

C. Naive Controls - Ten naive control guinea pigs were treated with 0.4 g of a 75% w/w mixture of the test substance in distilled water at challenge only in the manner described above.

II. RESULTS and DISCUSSION:

Reactions and duration - During the main test, 12/20 test animals exhibited very faint (grade 0.5) erythema during induction. Following challenge, 10/20 test animals

exhibited faint erythema (grade 1) and 3/20 test animals exhibited moderate erythema (grade 2) at the 24 hour observation. At the 48 hour observation, 4/20 animals continued to exhibit faint erythema and 2/20 animals moderate erythema. The test substance did not affect body weight gain.

B. Positive control - At both the 24 and 48 hour observations, 4/9 positive control animals exhibited very faint erythema (grade 0.5) and 4/9 positive control animals exhibited faint erythema (grade 1.0) at challenge. Three of the five naive control animals used in the validation study exhibited very faint (grade 0.5) at the 24 hour observation, persisting in 1/5 animals at the 48 hour observation.

C. Reviewers Conclusions: Agree with study author that this product is a dermal sensitizer.

D. Deficiencies – The following deviations are reported by the study author:
"1) The vehicle control group was not challenged using the vehicle during the challenge phase; 2) Body weights were not performed on weeks 2, 3, and 4 of the study and 3) clinical observations were not performed during the study."

ACUTE TOX ONE-LINERS

1. DP BARCODE: 323677
2. PC CODES: 067710
3. CURRENT DATE: 15/DEC/2005
4. TEST MATERIAL: Indoxacarb (DPX-MP062) 0.5RB; Batch number DPX-MP062-428; Lot Number: PLS-14-59; Purity: 0.5% Indoxacarb; brown gel

Study/Species/Lab Study # /Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity/rat Haskell Laboratory for Health and Environmental Sciences Dupont-16979/ 7-27-2005	46684604	Oral LD_{50} (Females) is greater than 5000 mg/kg bw	IV	A
Acute dermal toxicity/rat Haskell Laboratory for Health and Environmental Sciences Dupont-16980/ 7-07-2005	46684605	LD50 (males and females) >5000 mg/kg	IV	A
Acute Inhalation Toxicity Waiver Submitted	46684609	Waiver acceptable	IV	A
Primary Eye Irritation Haskell Laboratory for Health and Environmental Sciences Dupont-16983/6-17-2005	46684606	No corneal opacity, iritis or positive signs of conjunctivitis observed	IV	A
Acute Dermal Irritation Haskell Laboratory for Health and Environmental Sciences Dupont-16981/6-02-2005	46684607	No erythema or edema observed. PDI = 0.0	IV	A
Dermal Sensitization Product Safety Labs Dupont-16982/8-02-2005	46684608	Sensitizer	Yes	A

Core Grade Key: A =Acceptable, S = Supplementary, U = Unacceptable, W = Waived